take account of the fact that the islands of Langerhans are concerned not merely in the combustion of sugar or storage of glycogen, but also in the maintenance of the general tissues and reserves. In some manner an increased supply of fat or formation of adipose tissue imposes a burden on the island function, and reduction of any kind of food or of the body weight reduces the demand upon this function. This fact seems to indicate that the island hormone has both a catabolic and an anabolic role.[10]

As the diabetic deficiency is so much more prominent with regard to carbohydrate, it is possible that the function is directly related to this alone, and that other foods are concerned only indirectly through their influence upon carbohydrate metabolism, though this point remains unproved. Whether the relation be direct or indirect, the status of the pancreatic hormone in general metabolism and of the disturbance of general metabolism in diabetes is sufficiently important that treatment must be directed to it and is seldom successful if limited to restriction of carbohydrate alone.

BENZYL BENZOATE IN PEDIATRIC PRACTICE.

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The writer became interested in this subject several years ago when Dr. David I. Macht was first working with this interesting and useful preparation.

Macht showed that the action of the opium alkaloids on smooth muscle fiber bears a direct relation to the chemical structure of the drug. The morphin group tend to stimulate contraction and to increase the tonus of smooth muscle while the papaverin group tend to inhibit contraction and to relax the tonus. He showed, further, that the stimulating action, on the one hand, is due to the pyridin part of the molecules and the relaxing properties to the presence of the benzylic grouping in their molecules. A search was made for a substance with a benzyl radical which would have the same action on smooth muscle but be free from toxic and narcotic principles. Macht finally settled on benzyl benzoate, a well-known organic ester, in commercial use in the manufacture of perfumes.

Benzyl benzoate, Macht also determined, was largely excreted in the urine as hippuric acid.

On the smooth muscle, benzyl benzoate inhibits the rhythmic contractions, lowers the muscle tone and relaxes spasm. The action on the intestinal movements is similar to atropin, an inhibition of peristaltic action. On the uterus, gall-bladder and the urinary bladder the action is antispasmodic, inhibiting the contractions and causing relaxation. On the circulation the action is chiefly on the peripheral vessels, a fall in pressure due to the relaxing of the arterial muscles. As ordinarily administered the effect on the circulation may be disregarded, although it is given by mouth for its action on arterial hypertension. Ordinary doses do not affect the heart or respiration except as they may produce a quieting effect on the respiratory centers in certain pathologic states. Such doses do not affect the central nervous system and only very large doses affect the general musculature.

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[10] Taylor, A. E.: Tr. Coll. Phys., Philadelphia, 1916, xxxviii, 254. Cf. Rockefeller Institute Monograph, 1919, No. 11, p. 128.

Therapeutically, Macht found the uses of the drug to be very much those which would be anticipated, *i. e.*, the inhibition of peristalsis and the relaxation of the spasm of smooth muscle.

In infants and young children many distressing symptoms are caused by the great tendency to spasm of the smooth muscles, and a brief consideration of the uses of benzyl benzoate in pediatric practice may be of service in stimulating further study of this drug, which, it would seem, bids fair to become a permanent part of our armamentarium.

On general convulsive conditions its action is often most favorable. This, perhaps, would scarcely be expected, but the clinical results have been very striking in infants who were having repeated convulsive seizures. There are certain children, and there are certain conditions, which doubtless cause a similar condition in any child, in which general convulsions are brought on by reflex action from what appears to be very slight causes, the so-called spasmophilic diathesis in the instance first named. One or two illustrative cases will suffice.

1. An infant, four days old when first seen. Delivery had been normal but a circumcision had been performed immediately after birth. This wound had become infected, and what appeared to be a general septic condition resulted. At some time each day the temperature reached 104° or 105° F. Omitting other irrelevant details it may be stated that the child was having forty to fifty convulsive seizures a day. The slightest movement about it was sufficient to provoke an attack. During the physical examination the child was in a constant state of spasm. Lumbar puncture was tried but no fluid could be obtained. Four-drop doses of benzyl benzoate, sufficiently diluted, were given and later the dose was diminished to one or two drops at four-hour intervals. The effect was all that could be desired. The number of convulsive seizures was diminished to about half dozen a day, the child was able to nurse with comfort and it eventually made an uneventful recovery.

2. A child of three, of extremely nervous parents and very nervous

itself, with the history of frequent convulsions, ate a variety of indigestible articles of food and started in with convulsions at frequent intervals. The stomach and bowels were emptied, but the convulsions persisted. Benzyl benzoate was administered in ten-drop doses and a condition of quietude resulted.

The first trials by the author were in whooping-cough. This disease presents certain peculiarities, among which is the notoriously uncertain action of antispasmodic drugs. What quiets one child will have but little effect in another. Taken all in all, belladonna or atropin gives the best results in the greatest number of cases, but atropin is a drug which cannot be left indiscriminately in the hands of the ever-increasing careless, and the same is true of most of the other powerful antispasmodic drugs. Benzyl benzoate acts fairly well in many cases, lessening the number of attacks of coughing and so making the patient more comfortable. The action is, however, uncertain. In some instances the relief is striking while in others it is practically *nil*. This may be due to lack of knowledge in the dosage, and it may be that in the resistant cases larger amounts would produce the desired effect.

In cases of bronchial asthma and in spasmodic bronchitis the effect is most happy, and in the author's experience most certain of all the diseases in which he has used the drug. The wheezing case of bronchitis is almost always converted into one with easy, silent respiration while the asthmatic is rendered tolerably comfortable, and this without the undesirable concomitant effects of most of the drugs ordinarily employed.

In colic due to spasm of the gastric or intestinal muscles relief is usually prompt, and in hiccough, sometimes a very uncomfortable symptom in early life, the results are more satisfactory than with any other drug with which the author is acquainted. Of course, the transient hiccough so commonly seen in young infants rarely needs treatment. In only the more severe and prolonged attacks is anything needed.

Of more importance and worthy of thorough investigation is the use of benzyl benzoate in pylorospasm. Of course, one should differentiate the cases in which the spasm predominates from those in which the obstruction is chiefly due to hypertrophy. Many cases supposed to be the latter may be permanently relieved by the use of antispasmodics, and the author has a long list of such cases in which atropin or papaverin has been successfully used. In fact, atropin has proved so satisfactory that the trial of any substitute made but little appeal. There are, however, cases in which the amounts of atropin required to cause relaxation will produce slight toxic symptoms, such as dryness of the mouth and throat and dilatation of the pupils. In such cases benzyl benzoate is of service and it has been successfully used in others. While apparently non-toxic the taste and burning sensation make it more difficult of administration. For those unfamiliar with the correct dosage of atropin it is perhaps safer; but the fact remains that atropin poisoning rarely, if ever, kills and is not liable to occur except when simple directions cannot be followed.

In diarrhea in which there is excessive peristalsis, benzyl benzoate may be used to check the excessive movements, and it does not check secretion and it may eventually replace opium in cases in which there is a doubt as to the propriety of using opium.

In spastic constipation it is also of value. Curious cases of this are not infrequently met with in children, and may even find their way to the operating table. Atropin has been the chief reliance, but benzyl benzoate is of positive value. One instance may be cited:

3. A previously healthy fifteen months' old boy was taken suddenly in the early morning with severe pains in the abdomen, vomiting and a certain amount of prostration. Castor oil was immediately administered by the mother and an enema given resulted in a small stool. The castor oil was without effect. Following the enema there were no more bowel movements and a repetition later in the day brought away only a little mucus. The vomiting continued. He was first seen about thirty-six hours after the onset and after various drugs had been given without relief and the question of operation for obstruction had arisen. Ten drops of benzyl benzoate properly diluted were retained and in about an hour there was a copious evacuation, with immediate relief of pain and vomiting.

Several similar cases have been seen by the author in which atropin hypodermically in full doses gave relief; in one, a child of two, who was supposed to have an obstruction of the intestine. The child had eaten heartily of some dry, branny breakfast food. Some time later in the day there was vomiting and a bowel movement, great pain referred to the abdomen and prostration. Repeated enemas and purgatives gave no relief. When seen, thirty hours later, the child was greatly prostrated and a mass could be felt in the lower part of the epigastric region, somewhat to the right. A rectal examination brought away a small amount of fecal matter mixed with some particles of the food. A large dose of atropin gave relief and a large quantity of breakfast food was passed. It had evidently passed rapidly through the stomach and swelling in the intestine through the absorption of fluid and caused a spasm of the intestinal muscles above and below. The antispasmodic action of the atropin relaxed this, just as benzyl benzoate had caused relaxation in the case reported.

It hardly seems necessary to quote case histories illustrative of each phase of the usefulness of this drug. It would seem that in a remarkably short time its place has been definitely made and one can safely predict it will continue in use until replaced by something better, or, at least, newer. Its limitations are scarcely known as yet but may easily be surmised. The dosage offers the greatest difficulty.

The author's experience has been limited to the use of a stable preparation prepared by Mr. H. A. B. Dunning, of Hynson, Westcott & Dunning, of Baltimore. Adults may take a dram of this at intervals of four to six hours as in dysmenorrhea. Macht gives the adult dose as 20 minims, but this will be found to be too small in many instances. For children the dose may be scaled down. Assuming the adult dose to be suited to 150 pounds, use either the amount obtained by the fraction of the child's weight and 150 or use Young's rule of the age divided by the age plus 12. Apply either of these to 60 minims as the maximum dose (not necessarily) to 40 minims as an average dose and 20 minims as a minimum dose.

The drug is hot and unpleasant to most children and must be diluted with water, sweetened water or milk. Older children may take it dissolved in olive oil and put up in capsules, but plenty of water should be taken at the same time. Carminatives are recommended to make the dose more palatable, but their use is of questionable value. Ampoules of benzyl benzoate in olive oil may also be had for hypodermic use when very rapid action is desired. When given by this method the drug should be injected intramuscularly.

The drug seems non-toxic. The author observed an instance when a dram was given by mistake to a child of six years. Apart from a disagreeable burning sensation in the mouth, throat and epigastrium no ill effects were noted. Whether the effects of the drug wear off with continued use, *i. e.*, a tolerance established, has not been determined.

Conclusions. Benzyl benzoate is a valuable addition to the armamentarium of the pediatrist. It may be used in place of atropin wherever a relaxing effect is desired on spasm of smooth muscle.

The author has used it sufficiently to be able to recommend it in bronchial asthma, spasmodic bronchitis, gastric or intestinal colic, hiccough and spasmodic constipation.

It has been recommended by others in excessive peristalsis.

In whooping-cough its action is often most beneficial, but the results are uncertain, as is the case with all other antispasmodics in this disease.

In general convulsive conditions not dependent on organic lesions of the central nervous system, especially in the newborn, the drug will be found of benefit.

It is non-toxic but not particularly agreeable to take.